REMARKS

Claims 19-31 and 33-40 are pending. An Appendix of Pending claims is attached for the Examiner's convenience.

Claim 35 has been amended to correct a typographical error. The spelling of "electricaly" has been changed to "electrically".

By way of summary, the present invention is directed to compositions and methods useful in the detection of nucleic acids utilizing electron transfer mechanisms. The invention relies on electron transfer between an electron transfer moiety (ETM) present in a nucleic acid hybridization complex and an electrode. Thus, the invention utilizes an electrode with a covalently attached nucleic acid. Upon hybridization of a target sequence, a double-stranded hybridization complex is formed that contains an ETM, and detection proceeds with the input of an AC signal resulting in electron transfer between the ETM and the electrode. As noted in the specification at page 55, lines 3-25, this may occur in a variety of ways, including as a result of the ETM being attached to the target sequence or to a second single stranded nucleic acid that hybridizes to the target sequence.

Thus, in the present invention, the apparatus of the invention may comprise an ETM, or this may be added later during the assay, such that a hybridization complex comprising the ETM is formed.

It should also be noted that the conductivity or redox state of the spacer used to connect the nucleic acid and the electrode (i.e. either a conductive oligomer or an insulator) does not change during the assay; rather, the spacer forms a "pathway" for the electron between the ETM and the electrode. Accordingly, covalent attachment of the nucleic acid to the electrode is an important aspect of the invention.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 19-31 and 33-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the location of the electron transfer moieties (ETMs). The Examiner's position appears to be that the location of the ETM must be defined within the apparatus claims to render the claims definite. The Applicants respectfully disagree.

As outlined above, the ETM used in the methods need not be "attached to the apparatus". Rather, they can be added later, during an assay, such that the hybridization complex comprising the target sequence comprises at least one ETM. It is clear that the ETMs of the invention are generally attached to a nucleic

acid as outlined in the specification at page 40, line 26 through page 41, line 6; page 41, line 20 through page 42, line 28, page 44, line 3, through page 46, line 3 or, alternatively, can be added as hybridization indicators that are not covalently attached to the hybridization complex; see specification at page 56, lines 3-26.

Accordingly, the Applicants submit that the claims are sufficiently definite to meet the standards of 35 U.S.C. §112, second paragraph, and the rejection should be withdrawn.

Rejection under 35 U.S.C. §102(e)

Claims 19-31 and 33-40 are rejected under 35 U.S.C. §102(e) as being anticipated by Ribi et al.

Ribi et al. describes a system that utilizes at least four components: a substrate, a set of interdigitating electrodes, a polymerizable surfactant film that forms a crystalline structure, and at least one binding ligand ("a member of a specific binding pair").

Ribi's substrate is an insulative solid support (see column 3, line 19), and can be made of a variety of materials. Preferred embodiments utilize polystyrene (see column 4, line 36). It should be noted that polystyrene is not a conductive material, and is not used in Ribi et al. as such.

A "highly oriented polymerized surfactant film" (column 3, lines 19-20) is then added to the insulative substrate. This may be done covalently or non-covalently (see column 3, lines 37-41). This surfactant film is either electronically semi-conducting or variably conducting (see column 3, lines 21-22).

Binding members (i.e. for binding a target analyte) are then added to the surfactant film (sometimes also referred to in Ribi et al. as a lipid portion; see column 5, line 26). The binding members are generally added to the surfactant film by using a linker (see column 5, lines 25-56). These linkers are chosen depending on the "degree to which one wishes to perturb the electrical properties of the polymer" (see column 5, line 34-36). That is, as shown below, the mechanism of Ribi et al. relies on a change in the electromagnetic properties of the film as a result of the binding of a target analyte. Thus, Ribi et al. states that "[t]he more rigid and shorter the linker, assuming high affinity analyte binding, the greater the perturbation of the polymer upon binding of the specific binding member to its complementary member." (Column 5, lines 37-40).

In addition, this perturbation causes a change in the electrical properties of the surfactant due to the presence of dopants. These dopants (donors and acceptors) alter their orientation in response to the binding of the target analytes, thus causing the changes in the electrical properties of the film. See column 5, lines 59-64:

The orientation of the acceptor or donor molecule (dopant) with respect to the polymer lattice will affect the polymers' net electrical characteristics. The electrical properties of the film will be affected by analyte binding where the binding event causes a change in the orientation of the dopant molecule.

Generally, Ribi et al. appears to function in the following way. Upon binding of a target analyte, the electromagnetic properties of the film change (either its electronic or optical properties; see column 3, line 26) as a result of binding of a target analyte for detection. Therefore the film is the intervening medium between the two electrodes, and changes in the film's properties serve as the basis of the assay for the presence or absence of the target analyte.

Furthermore, in order to make this work (as shown in Figure 3, column 16, lines 27-31, and column 16, line 61 to column 17, line 42 ("Electrode Protection") of Ribi et al.), the electrodes must be electrically insulated from the aqueous medium using such things as parafilm, wax, nail polish, etc., so that direct electrical contact of two interdigitating electrodes does not occur. As the Examiner will appreciate, if there is direct electrical contact of the two electrodes through the aqueous media, the presence of charge carriers in the sample would provide two pathways for current flow: through the solution and through the film. Presumably this would be unacceptable.

Furthermore, Ribi et al. does not outline covalent attachment of anything, much less nucleic acids, to the electrode; rather, in Ribi et al., the surfactant is attached to the insulative substrate. As will be appreciated in the art, Ribi's disclosed methods of forming electrodes on the surfaces are non-covalent methods such as "painting" the electrodes onto the substrate (see the Examples, column 27, lines 5-10) and photoresist/etching methods (see column 10, lines 17-31).

As the Examiner is aware, the law is well established that in order to anticipate a claim, the prior art must disclose "each and every element"of the claimed invention. SSIH Equipment S.A.v. U.S. Inc. Int'l. Trade Commission, 218 USPQ 678, 688 (Fed. Cir. 1983). As stated by the Federal Circuit in In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990), "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." (Emphasis added). See also Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc., 33 USPQ2d 1496 (Fed. Cir. 1995).

However, Ribi et al. does not disclose either the covalent attachment of nucleic acids using a spacer to the electrode or the use of monolayers. In addition, with specific reference to claim 35, Ribi et al. does not teach an array of electrodes. Accordingly, the rejection is improper and should be withdrawn.

Attached hereto is a marked-up version of the changes made to the claims by the "Restriction and Amendment". The attached page is captioned **"Version with markings to show changes made."**

The applicants submit that the claims are now in condition for allowance and an early notification of such is respectfully solicited. If after review, the Examiner feels that there are further unresolved issues, the Examiner is invited to call the undersigned at (415) 781-1989.

The Commissioner is authorized to charge any addition fees which may be required, including extension fees or other relief which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our Order No. A-64558-1/RFT/ RMS /RMK).

Respectfully submitted,

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"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

Claim 35 has been amended as follows:

35. (Amended) An apparatus for the detection of target nucleic acids in a test sample, comprising:
    a) a test chamber comprising an array of electrodes, each electrode comprising a covalently attached single stranded nucleic acid and a passivation agent monolayer; and
    b) an AC/DC voltage source [electricaly] electrically connected to said test chamber.

APPENDIX OF PENDING CLAIMS

19. (Thrice Amended) An apparatus for the detection of target nucleic acids in a test sample, comprising:

a) a test chamber comprising a first and a second electrode, wherein said first electrode comprises a single stranded nucleic acid covalently attached to said electrode via a spacer, wherein said electrode further comprises a passivation agent monolayer; and

b) an AC/DC voltage source electrically connected to said first and second measuring electrodes.

20. (Twice Amended) An apparatus for the detection of target nucleic acids in a test sample, comprising:

a) a test chamber comprising a first and a second electrode, wherein said first electrode comprises a covalently attached single stranded nucleic acid, wherein said electrode further comprises a passivation agent monolayer and wherein said nucleic acid further comprises a covalently attached second electron transfer moiety; and

b) an AC/DC voltage source electrically connected to said test chamber.

21. An apparatus according to claim 19, 20 or 26, further comprising:

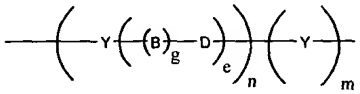
d) a processor coupled to said electrodes.

22. (Amended) An apparatus according to claim 19, 20 or 26, wherein said AC voltage source is capable of delivering frequencies from between about 1 Hz to about 100 kHz.

23. (Twice Amended) An apparatus according to claim 20, wherein said single stranded nucleic acid is covalently attached to said first electrode via a spacer.

24. An apparatus according to claim 23, wherein said spacer is a conductive oligomer.

25. (Twice Amended) An apparatus according to claim 19, 23 or 27, wherein said spacer is a conductive oligomer having the formula:



wherein

Y is an aromatic group;

n is an integer from 1 to 50;

g is either 1 or zero;

e is an integer from zero to 10; and

m is zero or 1;

wherein when g is 1, B-D comprises two atoms forming a bond able to conjugate with neighboring bonds; and

wherein when g is zero, e is 1 and D is selected from the group consisting of carbonyl and a heteroatom moiety, wherein the heteroatom is selected from oxygen, sulfur, nitrogen and phosphorus.

3 26. (Amended) An apparatus for the detection of target nucleic acids in a test sample, comprising:

a) a test chamber comprising a first and a second electrode, wherein said first electrode comprises a covalently attached first single stranded nucleic acid and a passivation agent monolayer;

b) a second nucleic acid covalently attached to a electron transfer moiety; and

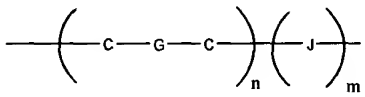
c) an AC/DC voltage source electrically connected to said test chamber.

9 27. (Amended) An apparatus according to claim 26 wherein said single stranded nucleic acid is covalently attached to said electrode via a spacer.

10 28. An apparatus according to claim 27, wherein said spacer is a conductive oligomer.

11 29. An apparatus according to claim 27, wherein said spacer is an insulator.

12 30. An apparatus according to claim 19, 23 or 27, wherein said spacer is a conductive oligomer having the formula:



wherein

C are carbon atoms;

n is an integer from 1 to 50;

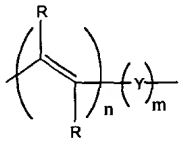
E

m is 0 or 1;

J is a heteroatom selected from the group consisting of nitrogen, silicon, phosphorus, sulfur, carbonyl and sulfoxide; and

G is a bond selected from single, double and triple bonds.

13 31. (Amended) An apparatus according to claim 19, 23 or 27, wherein said spacer is a conductive oligomer having the formula:



wherein

n is an integer from 1 to 50;

m is either zero or 1;

Y is an aromatic group; and

R is a substitution group.

14 33. (Amended) An apparatus according to claim 19, 20 or 26 wherein said passivation agent monolayer comprises conductive oligomers.

15 34. An apparatus according to claim 19, 20 or 26 wherein said passivation agent monolayer comprises insulators.

16 35. (Amended) An apparatus for the detection of target nucleic acids in a test sample, comprising:

a) a test chamber comprising an array of electrodes, each electrode comprising a covalently attached single stranded nucleic acid and a passivation agent monolayer; and

b) an AC/DC voltage source electrically connected to said test chamber.

17 36. An apparatus according to claim 35 wherein at least one of said single stranded nucleic acids is attached to said electrode via a spacer.

18 37. An apparatus according to claim 36 wherein said spacer is an insulator.

E

19 ~~38.~~ An apparatus according to claim 36 wherein said spacer is a conductive oligomer.

20 ~~39.~~ An apparatus according to claim 35 wherein said passivation agent monolayer comprises conductive oligomers.

21 ~~40.~~ An apparatus according to claim 35 wherein said passivation agent monolayer comprises insulators.